

**REMARKS**

Claims 13-18, 20-27, 29, 48-51, 52-60 and 61-65 have been amended. Claims 1-12, 19, 28, 30-47 and 66-74 have been canceled. Claims 48-49, 51-58 and 60-65 are withdrawn. Claims 13-18, 20-27, 29, 50 and 59 are currently examined in this application.

**35 U.S.C. § 103(a)**

Claims 13-18, 20-27 and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Deihl (WO 9413280) in view of Fassberg et al. (EP 0656206) in further view of Kanios et al. (U.S. Patent No. 5,719,197) or alternatively the Physicians' Desk Reference 1995 (PDR). This rejection is respectfully traversed.

Independent claims 13 and 21 recite methods of administering testosterone or a pharmaceutically acceptable ester thereof to a mammal, comprising spraying the oral mucosa of the mammal with a buccal spray composition comprising: testosterone or a pharmaceutically acceptable ester thereof and a non-polar solvent or a mixture of a polar and non-polar solvent.

The Office Action asserts that Deihl provides "general teachings of formulations for buccal mucosal administration" (Office Action at 5). The Office Action acknowledges, as it must, that Deihl fails to disclose testosterone, and also fails to disclose the use of the presently claimed solvents or amounts, including polyethylene glycol or non-polar solvents.

Based on the alleged "general teachings" of Deihl, the Office Action asserts that it would have been obvious to "have looked in the art for other specific solvents suitable for spray formulations of liquid carriers, as taught by Fassberg et al., with reasonable expectations of successfully preparing suitable formulations for various

therapies." (Office Action at 5). Because Fassberg et al. also fails to disclose or suggest testosterone, the Office Action relies on the lists of drugs set forth in Kanios et al. or the PDR, and asserts that "it is obvious to one of ordinary skill in the art to have substituted any suitable active agent for the analgesics of Deihl's buccal spray formulations as...taught by Kanios et al. or the Physicians' Desk Reference." (Office Action at 5, emphasis added).

Thus, the Office Action is premised on the PTO's reading of Deihl as a general teaching from which one may allegedly extrapolate to multiple other solvents and amounts, and to other pharmaceutically active agents, and do so with a reasonable expectation of success. Remarkably, this reasoning is based on Fassberg et al., which is not directed to buccal sprays, much less to propellant-free sprays as claimed, and on Kanios et al. and the PDR, which are not directed to buccal sprays at all. Aside from the shortcomings of these secondary references, Deihl itself is far from a general teaching of buccal sprays from which one of ordinary skill at the time of the present invention would have expected much of anything at all, much less that one of ordinary skill would have been motivated to modify Deihl to achieve the presently claimed methods for administering testosterone.

More specifically, at the time of the present invention, Deihl would not have been considered a credible or relevant teaching and, for the reasons discussed below, would not have been relied upon in any capacity by those skilled in the art at the time that the present invention was made. Deihl purports to teach a sprayable, therapeutic, analgesic composition where an analgesic is capable of being absorbed into the bloodstream through the buccal mucosa. Deihl's composition includes ibuprofen or acetaminophen and aqueous ethanol. Deihl states that for treatment of a headache, a patient sprays four measured sprays into the mouth. Each spray is 50 microliters and contains 1 milligram of acetaminophen or ibuprofen. This treatment may be repeated

once after five minutes. That is, Deihl teaches a total dose of 4-8 milligrams of acetaminophen or ibuprofen. Deihl at 5.

Even assuming 100 percent bioavailability, those of ordinary skill in the art would readily appreciate that a 4-8 milligram dose of acetaminophen or ibuprofen is not even remotely therapeutically effective. According to GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed., the oral dosage for acetaminophen is 320 to 1000 milligrams for adults and 40 to 480 milligrams for children with about 88% bioavailability. For ibuprofen the oral dosage for adults is 400 milligrams for mild pain to as much as 3200 milligrams for arthritis, with about 80% bioavailability. Thus, even assuming 100% bioavailability, a patient receiving Deihl's formulation would receive only 4-8 milligrams of active agent, a tiny fraction of what is required for any therapeutic effect. A patient would need to administer a completely unworkable number of spray activations of Deihl's formulation to realize any potential therapeutic effect, but by that point the volume of fluid sprayed would be so great as to result in swallowing and thus avoid mucosal absorption. Therefore, one of ordinary skill in the art would have readily appreciated that Deihl's buccal spray composition and method is unworkable and ineffective.

One of ordinary skill in the art would also have appreciated that Deihl's ineffective, unworkable spray teachings were quite consistent with the state of the art at the time the present invention was made. Those skilled in the art generally perceived buccal administration as an ineffective and unworkable delivery method. For example, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710, a copy of which is enclosed, states that "when only small amounts of drugs are required to gain access to the blood, the buccal route may be satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route." (emphasis added)

This well accepted view of buccal administration was based in part on the belief that the relatively rapid clearing of the mouth by swallowing limited the buccal absorption phase to between about 5-10 minutes. Therefore, it was understood that the amount of drug delivered would be very small causing the blood plasma levels of drugs administered buccally to rise slowly. Thus, buccal administration was generally disfavored and thought to be an ineffective and unworkable delivery method. Consequently, the disclosure of Deihl itself, as well as the general understanding in the art, were completely inconsistent with the Office Action's assertions and reasoning that Deihl provides a general teaching from which one of ordinary skill would have been motivated to extrapolate to diverse pharmaceutical actives and solvents, much less to do so with any expectation of success in administering testosterone via a buccal spray.

In addition, Fassberg et al. relates to an inhalation aerosol, which is a propellant-containing spray or powder formulation for oral and/or nasal administration. Fassberg et al. does not disclose or suggest any propellant-free method for the delivery of an active agent by spraying the buccal mucosa of a mammal. Fassberg et al. clearly does not teach or suggest that buccal administration of any actives, much less testosterone, is generally effective.

According to the PTO, it would have been obvious to modify Diehl with the solvents disclosed by Fassberg et al. (Office Action at 3-4.) To the contrary, one of ordinary skill would not have used the Fassberg et al. solvents to modify the formulations of Diehl, because Fassberg et al. explains that the solvents used in its inhalation formulations are only present to facilitate the propellant. Diehl has no propellant and the present claims exclude propellants. Accordingly, one of ordinary skill in the art would not have been motivated to modify Diehl with the teachings of Fassberg et al., for this additional reason.

Likewise, one of ordinary skill in the art would not have been motivated to modify Diehl with the teachings of Kanios et al. to achieve the compositions and methods recited by the presently pending claims. Kanios et al. refers to an intermediate composition that is made into a “finished dosage form” by applying a flexible backing which further defines the size and shape of the finished dosage form, which is, among other things, occlusive to water permeation *in vivo*. Kanios et al. is entirely unrelated to a buccal spray method for transmucosal administration.

Similarly, one of ordinary skill in the art would not have been motivated to modify Diehl with the PDR to achieve the methods recited by the presently amended claims. The PDR is cited for teaching a testosterone solution, and is unrelated to any buccal spray method for transmucosal administration. In fact, the PDR states that testosterone is administered by injection.

For at least these reasons, Applicant respectfully requests that this § 103 rejection be withdrawn.

Claims 13-18, 20-27 and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fu et al. (WO 9303751) in view of the PDR. This rejection is respectfully traversed.

Like Deihl, the Office Action uses Fu et al. as a general teaching from which one of ordinary skill could have allegedly extrapolated to any other pharmaceutical active, and have done so with an expectation of success, based on “the general teachings of formulations for buccal mucosal administration of Fu et al.” (Office action at 6). Again, the Office Action is mistaken, as Fu et al. is anything but a general teaching that would have motivated one of ordinary skill to look to the PDR with any

expectation of success, and the general state of the art at the time of the present invention was to the contrary (as discussed above, citing Remington).

Fu et al. refer to compositions for the sublingual delivery of specific polypeptides that are normally degraded upon oral administration. Fu et al. is directed to the administration of polypeptides that can not be ingested. These polypeptides are very limited in scope. Fu et al. only present examples of formulations containing leuprolide acetate and deslorelin acetate, which is closely related to leuprolide acetate. At most, Fu et al. establish that buccal administration can be used for specific polypeptides and only when a permeation enhancer is employed. See e.g., Fu et al. at 10-12 (showing low bioavailability for exemplary formulations, less than 25% bioavailability for all but one formulation). This underscores the general state of the art regarding the problem with buccal delivery as described by Remington.

The examples provided by Fu et al. are limited to two closely related polypeptides that can not be administered by oral ingestion. Thus, Fu et al. would not have been viewed as a general teaching for successful buccal administration of a variety of pharmaceutical actives. Therefore, one of ordinary skill in the art would not have been motivated to modify Fu et al. with any of the pharmaceutical actives of the PDR, as stated in the Office Action. For at least these reasons, Applicant respectfully requests that this rejection be withdrawn.

Claims 50 and 59 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fu et al. (WO 9303751) in view of the PDR in further view of Lee et al. (US 6,512,002). This rejection is respectfully traversed.

Lee et al. relates to compositions useful in treating conditions responsive to the elevation of testosterone, including stimulation of erythropoiesis. Lee et al., however, does not disclose any buccal spray.

Claims 50 and 59 depend from independent claims 13 and 21, respectively and further recite stimulating erythropoiesis in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of the buccal spray of claim 13 or 21, respectively. As discussed above in connection with the rejection of claims 13-18, 20-27 and 29, one of ordinary skill in the art would not have been motivated to combine Fu et al. and the PDR. Like the PDR, Lee et al. does not relate to buccal sprays. Accordingly, for the same reasons discussed above, one of ordinary skill in the art would not have been motivated to combine Lee et al. with Fu et al. and the PDR. In fact, those of skilled in the art would have had no expectation of success in stimulating erythropoiesis via a buccal spray containing testosterone based on any of the teachings in Fu et al., the PDR and Lee et al. For at least these reasons, withdrawal of this rejection is respectfully requested.

#### **Double Patenting**

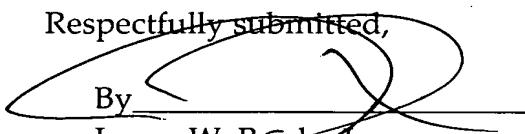
Claims 13-18, 20-27, 29, 50 and 59 are provisionally rejected over claims of several co-pending applications. As the claims of the present application, as well as those of the co-pending applications are subject to change, Applicant respectfully requests that the provisional rejections be held in abeyance until such time as this or a co-pending application is in a condition for allowance.

#### **Examiner's Note**

The Office Action states that certain concentration ranges in the claims do not correspond to concentration ranges stated in the application. Applicant has broadened the claimed ranges as set forth in the Specification.

In view of the above, Applicant believes the pending application is in condition for allowance. If the Examiner should believe that anything further may be required to place this application in even better form for allowance, she is cordially invited to telephone the Applicant's undersigned representative.

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Respectfully submitted,  
  
By \_\_\_\_\_  
James W. Brady, Jr.  
Registration No.: 32,115  
Elizabeth Parsons  
Registration No. 52,499  
DICKSTEIN SHAPIRO LLP  
1825 Eye Street, NW  
Washington, DC 20006-5403  
(202) 420-2200

Enclosure